

The University of Chicago

A STUDY
OF SOME ALDEHYDE REACTIONS

A DISSERTATION SUBMITTED TO THE FACULTY
OF THE DIVISION OF THE PHYSICAL SCIENCES
IN CANDIDACY FOR THE DEGREE OF DOCTOR
OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY
MARCH, 1941

By
ISADORE RICHLIN

CHICAGO, ILLINOIS

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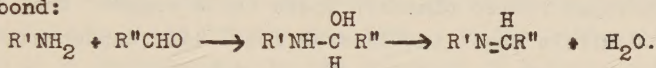
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I. THE CONDENSATION OF BUTYRALDEHYDE AND ANILINE

The Reaction in Neutral Medium

The reaction between primary amines and aldehydes is assumed to follow the same course as do other reactions involving carbonyl compounds and ammonia derivatives, namely, the addition of the amine to the carbonyl double-bond. Compounds of this type have been isolated.¹ Water is then eliminated from the intermediate compound with the establishment of a carbon-to-nitrogen double-bond:



The structure of the Schiff's base and the presence of the azomethine bond has been demonstrated by (a) reduction, (b) hydrolysis, and (c) hydrogen cyanide addition (with subsequent hydrolysis of the nitriles to amides and acids).² The azomethine bond exhibits many of the properties of the carbonyl bond; thus, it will add hydrogen cyanide, hydrogen sulfide, sodium bisulfite, and Grignards.³

Schiff's bases also undergo polymerization, and two types of structure have been proposed for the polymers: ring and open-chain. Satisfactory evidence is available that the trimeric Schiff's bases, that is, polymers of the Schiff's bases formed from formaldehyde, are cyclic in nature. The work of Bischoff, who first proposed this structure, has recently been confirmed.⁴

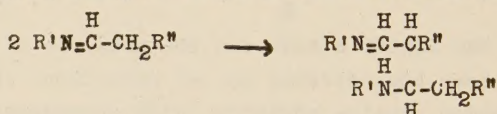
¹Dimroth and Zoeppritz, Ber., 35, 984 (1902).

²Mailhe, Bull. soc. chim. (iv), 25, 321 (1919); O. Fischer, Ber., 19, 748 (1886); Ann., 241, 328 (1887); Schiff, Ann., Suppl. 3, 343 (1864); Miller and Flochl, Ber., 25, 2020 (1892); ibid., 31, 2700 (1898).

³Miller and Flochl, ibid., 25, 2027 (1892); Eibner, Ann., 316, 108 (1901); Knoevenaegel, Ber., 37, 4083 (1904); Bucherer and Schwalbe, ibid., 39, 2796 (1906); Ekeley and Swisher, Rec. trav. chim., 48, 1052 (1929); Busch, Ber., 37, 2691 (1904); Busch and Rinck, ibid., 38, 1761 (1905); Mayer, Bull. soc. chim. (iii), 33, 157, 395 (1905).

⁴Bischoff, Ber., 31, 3248 (1898); Miller and Wagner, J. Am. Chem. Soc., 54, 3698 (1932).

The structure of the dimeric Schiff's bases is unsettled. A cyclic structure for compounds of this type has been proposed by Ingold and Piggott.⁵ Their conclusions, however, seem to be based on insufficient chemical evidence. The molecular weight determinations of the compound used in favor of their formulation have since been shown to be incorrect.⁶ There is, then, no well established evidence for the cyclic structure for dimeric Schiff's bases. In our opinion, the aldol type structure for these compounds is most satisfactory.⁷ Miller and Plochl were the first to point out that Schiff's bases of formaldehyde formed trimers, that those from aromatic or alpha-beta unsaturated aldehydes did not polymerize, while those from aldehydes containing a labile alpha-hydrogen formed dimers. These facts suggest that dimerization of Schiff's bases involves an aldol-like condensation:



The extensive researches of Eibner, while not absolutely conclusive, lend much credence to the Miller-Plochl interpretation of the dimerization of Schiff's bases.⁸

Discussion of Results

When equimolar quantities of freshly distilled n-butyraldehyde and aniline are mixed together, an immediate and vigorous reaction takes place. Two products have been isolated from this reaction. Rampini reported the formation of a monomeric Schiff's bases (isolated as the HCN addition product), and Williams described a dimer.⁹ We have confirmed the dimeric nature of the compound so characterized by Williams. It is a white crystalline material of melting point 92.5°. Molecular weight determinations

⁵J. Chem. Soc., 121, 2793 (1922); *ibid.*, 123, 2745 (1923); *ibid.*, 125, 87 (1924); *ibid.*, 127, 1141 (1925).

⁶Miller and Wagner, *op. cit.*

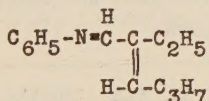
⁷Miller and Plochl, *Ber.*, 25, 2020 (1892); *ibid.*, 27, 1281 (1894); *ibid.*, 29, 1462 (1896).

⁸Eibner, *ibid.*, 27, 1296 (1894); *ibid.*, 33, 3658 (1900); *Ann.*, 302, 335 (1898); *ibid.*, 318, 58 (1901); *ibid.*, 328, 121 (1903); *ibid.*, 329, 210 (1903).

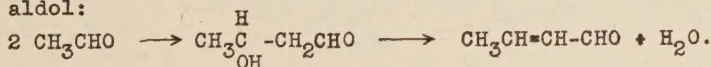
⁹Rampini, *Ber.*, 25, 2038 (1892); Williams, U. S. Patent 1908093 (May 9, 1933; *C. A.*, 21, 3854 [1933]).

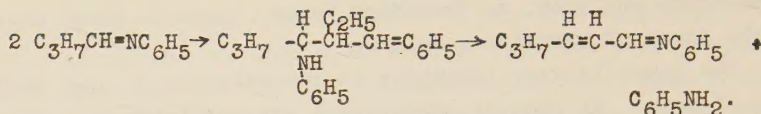
and elementary analyses, as described below, leave no doubt that it is the dimer of butylidene aniline.

The dimer is very sensitive to the presence of even small amounts of acid. If special precautions are not taken to insure that the butyraldehyde is acid-free, or if as little as 0.03 mole per cent of butyric acid be added to the reaction mixture, a yellow oil is formed, rather than the dimer. Rampini, who prepared his aldehyde by an acid hydrolysis of the sodium bisulfite addition product, so that his aldehyde might have contained some acid, noted but did not study this oil. His failure to obtain the crystalline dimer may have been due to the acidity of his aldehyde. This yellow oil may also be obtained by treating the pure dimer with small amounts of organic acids or by letting the dimer preparation stand for several days. In the latter case, the reaction is probably due to the presence of butyric acid formed by air oxidation of the butyraldehyde. We have investigated this oil fully. Molecular weight determinations and elementary analysis show that it consists of one molecule of aniline combined with two molecules of butyraldehyde, less two molecules of water. It is formed from the dimer by the loss of one molecule of aniline per mole of dimer. The following reactions show that this oil is the monomeric Schiff's base of aniline and α -ethyl- β -propylacrolein. Treatment of the oil with benzoyl chloride and acetyl chloride gave respectively benzanilide (93% of theory) and acetanilide (60%), while treatment with 2,4-dinitrophenylhydrazine and semicarbazide hydrochloride gave the corresponding hydrazone (83% yield) and semicarbazone (60%) of α -ethyl- β -propyl acrolein. Since identical products were prepared from pure, known α -ethyl- β -propylacrolein, the above is satisfactory evidence that the structure of the oil is best represented by the following structure:



An open-chain structure for the dimer best explains the formation of the oil. If we accept the formation of the dimer as an aldol-like condensation, the formation of the oil from the dimer is closely analogous to the formation of crotonaldehyde from aldol:





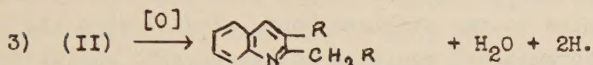
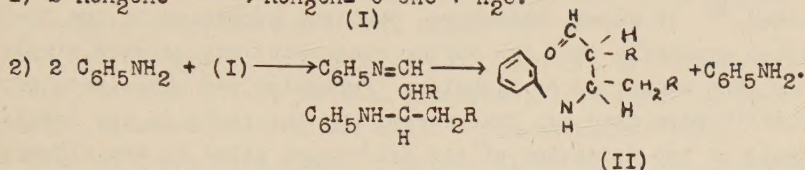
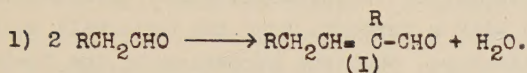
Eibner was able to demonstrate the presence of a secondary amine nitrogen in Schiff's base dimers. We have been able to show the presence of an azomethine bond to account for the other nitrogen atom. This has been done by a quantitative catalytic hydrogenation under one hundred atmospheres pressure to a diamine, from which we have prepared a diacetyl derivative and a dihydrochloride. Furthermore, the fact that only one mole of hydrogen need be taken up to form a diamine is compatible with the proposed structure for the dimer. That the dimer, like aldol, is able to break down to the monomer and then recondense we have shown in several ways. The boiling point of the dimer is lower than that of the oil; the obvious conclusion is that some breakdown to the monomer has occurred. Furthermore, the pure dimer boiled over a range of about fifty degrees. Finally, the molecular weight determinations by Rast's method in camphor, some eighty degrees above the melting point of the dimer, showed 40-50 per cent depolymerization, while the same technique in triphenylmethane, at about the melting point of the dimer, gave values closely approximating those calculated for the dimer.

The Reaction in the Presence of Acid

The most general reactions for the preparation of quino-line and its derivatives consist of the condensation of primary aromatic amines and aldehydes and ketones, either pre-formed or formed in the reaction, in the presence of strong mineral acid.¹⁰ The most widely accepted mechanisms have been described by Sidgwick.¹¹ The commonly accepted mechanism for the Doebner-Miller Synthesis is as follows:

¹⁰Skraup, *Monatsh.*, 1, 316 (1880); Doebner, Miller, et al., *Ber.*, 14, 2812 (1881); *Ibid.*, 16, 2464 (1883); *ibid.*, 17, 1698 (1884); *ibid.*, 18, 3361 (1885); *ibid.*, 24, 1720, 2072 (1891); Beyer, *J. prakt. Chem.* (2), 33, 393 (1886).

¹¹N.V. Sidgwick, *The Organic Chemistry of Nitrogen* (Oxford, Oxford University Press, 1937), pp. 544 ff.

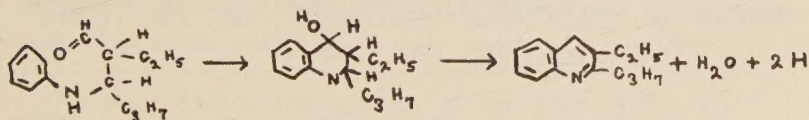
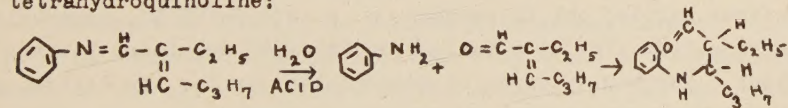


Our work has been concerned mainly with the Doebner-Miller synthesis, but some of our conclusions are applicable to the Skraup and Beyer syntheses.

It is claimed that the condensation of n-butyraldehyde and aniline in the presence of concentrated hydrochloric acid yields 2-propyl-3-ethyl-quinoline and N-butyraniline:

$$2 \text{ C}_6\text{H}_5\text{NH}_2 + 3 \text{ C}_3\text{H}_7\text{CHO} \longrightarrow \text{quinoline derivative} + \text{C}_6\text{H}_5\text{NC}_4\text{H}_9 + 2\text{H}_2\text{O}.$$

Considerable high-boiling material is also obtained. 2-Propyl-3-ethyl-quinoline may also be formed in varying yields (see experimental part) by the action of strong hydrochloric acid on butylidene aniline dimer (a compound whose structure we have shown to be identical with Sidgwick's hypothetical beta-anilino-anil), on a mixture of α -ethyl- β -propyl acrolein and aniline, and on the anil of α -ethyl- β -propylacrolein, the oil formed from the dimer. We believe that the latter reaction, which seems at first glance to be remarkable, can best be explained on the basis of (a) hydrolysis of the oil to aniline and α -ethyl- β -propylacrolein, (b) addition of the aniline to the unsaturated aldehyde, (c) ring closure between the carbonyl group and the alpha-hydrogen atom of the ring with elimination of water, and (d) transfer of hydrogen from at least part of the dihydroquinoline formed to other molecules, forming a substituted quinoline and tetrahydroquinoline:



That aniline, in the presence of its hydrochloride, will add to double-bonds conjugated with a carbonyl bond has been well established.¹² It seems, therefore, that the mechanism of the Doebner-Miller synthesis (and the Skraup synthesis) may be more simple than that described by Sidgwick. Formation and hydrolysis of the Schiff's base need not take place; and the reaction may consist simply of the formation of the dehydrated aldol of the aldehyde, addition of the amine to the ethylene bond, ring closure and oxidation. This formulation would be in accord with our observation that the azomethine bond in the Schiff's base dimers is less readily hydrolyzed than the secondary amine nitrogen-to-carbon bond.

Experimental Part

The preparation of butylidene aniline dimer.--Aniline, freshly distilled from zinc dust in vacuo, and freshly distilled n-butyraldehyde are mixed in equimolar proportions. The immediate separation of water and the evolution of heat require constant stirring and cooling under the water-tap. The flask is stoppered and allowed to stand for eighteen to twenty-four hours, by which time the reaction mixture is an almost solid mass of the crystalline dimer. This is recrystallized from alcohol. The best yield is obtained when the utmost precautions are observed to avoid the presence of acid; this has been accomplished by adding to the reaction mixture a small amount of aqueous sodium carbonate and by adding the same to the recrystallization medium. Yields up to 78 per cent of the product melting at 92.5° have been obtained.

Anal. Calcd. for $C_{20}H_{26}N_2$: C, 81.61; H, 8.88; N, 9.51. Found: C, 81.49, 81.75; H, 8.88, 8.89; N, 9.41, 9.64.

Molecular weight determinations.--The average of ten molecular weight determinations by Rast's method at two different concentrations in triphenylmethane is 281.4 (± 12), compared with the value of 294.4 calculated for the dimer.¹³ The same determinations carried out in camphor, m. p. $176.7-176.9^{\circ}$, gave values varying from 176 (5% solution) to 251 (10% solution) for the dimer. Further evidence of dissociation is the low boiling point,

¹²Lapworth et al., J. Chem. Soc., 121, 2741 (1922); Hickinbottom, *ibid.*, 2646 (1932); *ibid.*, 319, 1981 (1934).

¹³Rast, *Ber.*, 55B, 1051 (1922).

130-80°/25 mm., and the range. If water and acid be excluded, up to 75 per cent of pure crystallized material may be recovered from a vacuum distillation of the dimer.

Hydrogenation of the dimer.--By the use of a nickel catalyst and hydrogen at one hundred atmospheres pressure, we have succeeded in hydrogenating the dimer in quantitative yield.¹⁴ The hydrogenated dimer is a heavy, viscous oil of b. p. 240-5°/20 mm. It forms a diacetyl compound of m. p. 131°.

Anal. Calcd. for 1,3-diacetanilido-2-ethylhexane, $C_{24}H_{31}N_2O_2$: N, 7.24. Found: N, 7.47.

Anil of α -ethyl- β -propylacrolein.--In the presence of small amounts of organic acid, as when old butyraldehyde is used, or as when as little as 0.03 mole per cent of acetic or butyric acid is added to the reaction mixture, the product from the condensation of butyraldehyde and aniline is a yellow oil of b. p. 146-8°/15 mm. The crystalline dimer may or may not precipitate during the course of the reaction. Similarly, if an acid-free preparation is allowed to stand in the air for several days, the oil is formed, presumably due to the acid formed by air oxidation of the butyraldehyde. The crystals are stable for much longer periods when the reaction is carried out in tubes from which the air is carefully evacuated. That acid and not air is responsible for the instability of the dimer is shown by the rapid decomposition of the crystals in the presence of acid and absence of air. Analyses show that the oil differs from the dimer by one molecule of aniline per mole.

Anal. Calcd. for $C_{14}H_{19}N$: C, 83.47; H, 9.57; N, 6.96. Found: C, 83.64; H, 9.40; N, 6.95, 6.97.

A series of ten concordant determinations, some by Rast's method in triphenylmethane and some in freezing benzene by Beckmann's method, give an average value of 208.4 (± 15) compared with the calculated value of 201.3.

Treatment of the oil in benzene with excess benzoyl chloride at room temperature gives a 93 per cent yield of benzanilide. Treatment of the oil with excess acetyl chloride in hot pyridine gives a 60 per cent yield of acetanilide. The identities of these compounds were confirmed by melting points and mixed melting points with known samples.

¹⁴Covert, Connor, and Adkins, J. Am. Chem. Soc., **54**, 1651 (1932).

The use of 2,4-dinitrophenylhydrazine-sulfuric acid reagent according to the directions of Ferrante and Bloom results in the production, either from the oil or from α -ethyl- β -propylacrolein of the 2,4-dinitrophenylhydrazone of the latter.¹⁵ In either case, the yield is 83 per cent of theory. The melting point of both substances is 119-20°, and mixed melting points demonstrate their identity. Similarly, a hot aqueous solution of semicarbazide hydrochloride reacts with either the oil or α -ethyl- β -propyl acrolein to give the known semicarbazone of melting point 132°.¹⁶ The yield from the oil is 60 per cent and the identity of the two semicarbazones is shown by mixed melting point.

Synthesis of the anil of α -ethyl- β -propylacrolein from aniline and α -ethyl- β -propylacrolein.-- α -ethyl- β -propylacrolein was prepared from butyraldehyde in 58 per cent yield by the method of Raupenstrauch.¹⁷ It boiled at 171-2°/747 mm. When equimolar amounts of aniline and the acrolein were mixed, reaction took place within five minutes, as shown by the separation of water. After standing for two days, distillation of the mixture gave 70 per cent yield of a product of b. p. 146-8°/15 mm. Reactions of this compound with benzoyl chloride, acetyl chloride, semicarbazide hydrochloride, and 2,4-dinitrophenylhydrazine gave the same derivatives as those obtained from similar reactions with the oil from aniline and butyraldehyde.

Preparation of 3-ethyl-2-propylquinoline.--We have used as a reference material the 3-ethyl-2-propylquinoline formed by the method of Kahn and purified through the picrate by the method of Spady.¹⁸ Our product boils at 182-4°/23 mm. The boiling point recorded by Kahn was 290-2° at atmospheric conditions. Yields by this and other methods are recorded in Table 1. In each case, the reaction proceeded for from twenty to twenty-four hours at room temperature and 0.05 mole of aldehyde or its equivalent was used.

Identification and determination of 3-ethyl-2-propylquinoline.--The quinoline, either pure or in a mixture, was di-

¹⁵Ferrante and Bloom, Am. J. Pharm., 105, 381 (1933).

¹⁶Weizmann and Garrard, J. Chem. Soc., 117, 324 (1920).

¹⁷Monatsh., 8, 112 (1887).

¹⁸Kahn, Ber., 18, 3361 (1885); Spady, ibid., 3373 (1885).

TABLE 1
PREPARATION OF 3-ETHYL-2-PROPYLQUINOLINE

Form of Reactants	Mols of HCl per Mol Aniline ^a	Yield of 3-ethyl-2-Propylquinoline
Aldehyde and Amine ^{b,c} ..	0.1	20%
Aldehyde and Amine	0.5	58
Aldehyde and Amine	1.0	79
Aldehyde and Amine	1.5	60
Aldehyde and Amine	2.0	56
Aldehyde and Amine	5.0	54
Butylidene Aniline Dimer	1.0	50
α -Ethyl- β -propyl- acrolein	2.0	10
Anil of α -ethyl- β - propylacrolein	2.0	15
Aniline and the anil of α -ethyl- β - propyl- acrolein	1.0	20

^aThe HCl used was concentrated aqueous reagent, of approximately 12 N. The use of both anhydrous liquid HCl and of the concentrated acid diluted 20:1 gave poorer yields.

^bThe aldehyde and amine were present in proportions of 2:1, in accordance with the directions of Kahn, although the reaction requires only 3:2 proportions in accordance with the equation on page 5. It was found, however, that the use of 3:2 proportions did not vary the yield significantly.

^cThe best yields are obtained when the aldehyde and amine are first mixed together and the hydrochloric acid then added. Adding the hydrochloric acid over a period of either five minutes or thirty minutes gave the same results.

luted with about one-third its volume of 95 per cent alcohol. It was then treated with an excess of saturated alcoholic picric acid. The picrate precipitated immediately. After recrystallization from alcohol the picrate melts at 161-3°. We have been able to use this as a quantitative method.¹⁹ Analyses of mixtures containing zero to four parts by weight of aniline to 3-ethyl-2-propyl quinoline have yielded 98 to 100 per cent of the theoretical picrate. In general, better results are obtained if the quinoline fraction is separated from the tars by distillation before the determination.

¹⁹Cf. Schopf and Lehmann, Ann., 487, 16 (1932).

By-products of the 3-ethyl-2-propylquinoline preparation.--The reaction-mixture of the Doebner-Miller synthesis, when distilled, gives, besides the water and unchanged reagents (all of which distill below 120° at 15 mm.), two rather well defined fractions. The first, b. p. $120-200^{\circ}$ consists of N-n-butylaniline and 3-ethyl-2-propylquinoline; the second, b. p. over 200° at 15 mm., is made up of tarry materials which may contain tetra- and di-hydro quinolines (whose homologues have been previously reported as being present in other Doebner-Miller syntheses) and complicated polymerization products. We have confirmed the presence of N-butylaniline (67 per cent of yield predicted on basis of ethylpropylquinoline formed) as a by-product by the formation of its hydrochloride, m. p. $112-14^{\circ}$ (recorded, 114°),²⁰ and N-butyl-N-phenyl N'- α -naphthylurea, m. p. 277° . The hydrochloride gave neutral equivalents of 181, 182, and 185, compared with a calculated value of 185. The naphthylurea, a new compound, was prepared by the method of French and Wirfel,²¹ and it has the same m. p. as that formed from known N-butyl-aniline. A mixed melting point showed no depression.

Anal. Calcd. for the N-butyl-N-phenyl-N'- α -naphthyl urea, $C_{21}H_{22}N_2O$: N, 8.80. Found: N, 9.03.

In attempting to form the methiodide 3-ethyl-2-propylquinoline of melting point 172, described by Kahn,²² we were able to isolate a material of this melting point. This compound, however, was unstable and gave neutral equivalents on titration with alkali varying from 320 to 381 (theoretical for the hydroiodide is 341), showing that it was not a quaternary salt. When we attempted to form the methiodide from highly purified quinoline (through the picrate as above described), the material formed had a m. p. $160-65^{\circ}$ and was not titratable with alkali. This is probably the true quaternary methiodide.

Anal. Calcd. for 3-ethyl-2-propylquinoline methiodide, $C_{15}H_{20}NI$: I, 37.28. Calcd. for 3-ethyl-2-propylquinoline hydroiodide, $C_{14}H_{18}NI$: I, 38.63. Found (by Fajan's method): I, 37.11.

That the other compound was probably the quinaline hydroiodide tertiary amine was shown by its formation on passing an-

²⁰Braun and Murjahn, Ber., 59, 1202 (1926).

²¹J. Am. Chem. Soc., 48, 1736 (1926).

²²Ber., 18, 3361 (1885).

hydrous hydrogen iodide through a low-boiling ligroin solution of the pure quinoline. The melting point of this hydroiodide was $171-2^{\circ}$ and the material was titratable with base. A mixed melting point with the material originally isolated from treatment with methyl iodide was $169-71^{\circ}$.

Summary

1. The condensation of butyraldehyde and aniline in acid and neutral media has been studied.

2. The structure of the dimer of butylidene aniline has been established as well as that of the compound formed from it by the loss of aniline.

3. 3-ethyl-2-propylquinoline has been prepared in several ways. A mechanism has been suggested for the Doebner-Miller synthesis.

4. The following new compounds have been prepared: the anil of α -ethyl- β -propylacrolein, 1,3-diphenylamino-2-ethylhexane, its diacetyl derivative, α -ethyl- β -propylacrolein-2,4-dinitro-phenylhydrazone, N-butyl-N-phenyl-N'- α -naphthylurea, and 3-ethyl-2-propylquinoline hydroiodide and methiodide.

II. SOME FACTORS INFLUENCING THE RATE OF CANNIZZARO REACTION OF BENZALDEHYDE

Introduction

In the course of their classic research on the benzoyl radical, Liebig and Wohler studied the action of concentrated alkali on benzaldehyde.¹ They found among the products benzoic acid and an unknown oil. Two decades later Cannizzaro showed that the oil was benzyl alcohol and that the reaction was an inter-molecular oxidation-reduction.² During the century which followed the original investigation, considerable research has been concerned with this reaction.³

Recent work in these laboratories has been concerned with the study of some of the factors influencing the heterogeneous Cannizzaro reaction of benzaldehyde. Preliminary studies indicated that the extent and speed of the reaction were proportional to the peroxide content of the aldehyde.⁴ Further investigation failed to confirm this conclusion. It was found, however, that aldehydes purified by several vacuum distillations reacted at much lower rates than aldehydes not so purified.^{5,6} It was found impossible to correlate the peroxide content of the aldehyde, as

¹Ann., 3, 261 (1832). ²Ibid., 88, 129 (1853).

³Extensive reviews of the literature are to be found in the following theses of the Department of Chemistry, University of Chicago: Chenicek, "The Cannizzaro Reaction of Aromatic Aldehydes" (Unpublished Ph. D. dissertation, Dept. of Chemistry, University of Chicago, 1937); Radovsky, "A Study of the Cannizzaro Reaction" (Unpublished S. M. thesis, Dept. of Chemistry, University of Chicago, 1935). In addition, an excellent review of the work on the kinetics of the reaction appears in the articles by Eitel and Lock, Monatsh., 72, 392, 410 (1939).

⁴Kharasch and Foy, J. Am. Chem. Soc., 57, 1510 (1935); Foy, "The Cannizzaro Reaction of Aromatic Aldehydes as a Function of Peroxide Content" (Unpublished Ph. D. dissertation, Dept. of Chemistry, University of Chicago, 1936).

⁵In no case is the term "rate" used in its strict kinetic sense. In this paper rates are indicated by the observed percent reaction in a given time at a given temperature.

⁶Chenicek, "The Cannizzaro Reaction"

determined by titration, with the rate of reaction. Further, the addition of peroxides or of peroxide-forming materials did not raise the rate consistently; nor did the addition of antioxidants lower the rate of reaction.

Chenicek, in his study of the several variables of the reaction in heterogeneous solution, came to the following conclusions:

1. Concentration of reactants.--The concentration of potassium hydroxide solution used, and the molar proportions of the two reactants, influenced the rate of reaction. The source of the alkali was immaterial, since U. S. P., C. P., and Analytical grades were identical in effect so long as the concentration, as determined by titration, was kept constant.

2. Temperature.--The temperature coefficient was much less for the heterogeneous reaction than for the homogeneous reaction. Chenicek found the coefficient to be 1.8 per 40° between 0° and 40° , while Geib found a gradient of 1.9 per 10° for the homogeneous reaction.⁷

3. Volume of reactants and vessel.--It was found that an increase in the volume of the reaction tubes, while the volume of reactants was kept constant, resulted in an increase in rate; on the other hand, increase of the volume of the reaction mixture (by the use of an inert solvent) while the volume of the reaction vessels was kept constant, resulted in a decrease of the rate. This result seemed to be correlated with the effectiveness of agitation.

4. Light.--Chenicek found that aldehyde which had been exposed to mercury-vapor arc light reacted much faster than non-irradiated aldehyde.

Chenicek's observation on the effect of light on the reaction was of particular interest in view of the great amount of work which had been done previously on the effect of light on benzaldehyde, particularly with regard to auto-oxidation.⁸ Backstrom's work, as well as Mascarelli's, seemed to indicate the formation of a carbonyl free radical. There were many confirma-

⁷Geib, Z. physik. Chem., A169, 41 (1934).

⁸Ciamician and Silber, Ber., 36, 1575 (1903); Mascarelli, Gazz. chim. Ital., 3611, 670 (1906); Mascarelli and Bosinelli, Ibid., 421, 82 (1912); Kailan, Monatsh., 33, 1305 (1912); Hemptinne, Compt. rend., 186, 1295 (1928); Raymond, J. chim. physique, 28, 322, 480 (1931); Backstrom, Z. physik. Chem., 25B, 111 (1934); Luhn and Meyer, Naturwissenschaften, 16, 1028 (1928).

tions of the discovery that light was an accelerator for the auto-oxidation of benzaldehyde, while both Raymond and Kuhn and Meyer found that benzaldehyde carefully purified by "aseptic" distillation in the dark would not undergo auto-oxidation at all. The present paper concerns itself mainly with the discovery in these laboratories that light of the near ultra-violet and shorter wavelengths is a powerful accelerator for the heterogeneous Cannizzaro reaction of aldehydes.

Experimental Methods

Benzaldehyde.--The benzaldehyde used in this investigation was F. F. C. quality obtained from van Ameringen-Haebler, Incorporated, in one-pound lots packaged in amber bottles. The essential step in the purification of the aldehyde was a slow distillation carried out in the dark in high vacuum. Aldehyde which had previously been distilled at 10 to 20 mm. was placed in a 125 c.c. bulb connected by a yoke of 24 mm. pyrex tubing to the receivers. The apparatus was sealed to the vacuum line by means of eight mm. pyrex tubing. The aldehyde was cooled by means of a CO_2 -acetone bath to about -80° and the apparatus evacuated to less than 10^{-3} mm. pressure. The apparatus was then closed off from the line and the aldehyde allowed to come to room temperature, at which time the gasses trapped in the aldehyde were removed by warming. The aldehyde was again cooled to -80° , and the apparatus opened to the line. The system was then exhausted to 10^{-5} mm. pressure. From this point on, the aldehyde was protected from all light. After evacuation, the apparatus was sealed off from the line and removed to the darkroom. The aldehyde was then allowed to warm to room temperature or heated to $70-80^\circ$ with water in a Dewar flask, while the receivers were cooled in CO_2 -acetone. Any inspection of the distillation was carried out by the light of a small red mazda bulb six feet from the material. This aldehyde reacted to the extent of 5 to 15 per cent in an hour at 25° with the alkali described below. Any aldehyde which reacted faster was considered to be impure and was discarded.

Potassium hydroxide.--The alkali used was C. P. potassium hydroxide in pellet form, minimum 85% KOH. In all experiments, an aqueous solution of 48.2% KOH, 12.96 N, was used. In order to insure complete reproducibility two separate pipettes, one used exclusively for the alkali and one used only for the aldehyde, were employed. The alkali was stored in a paraffined bottle, and

titration of the last portions used showed less than 0.1 per cent variation from the original normality.

Agitation and temperature control.--Since the thoroughness of the mixing seemed to depend upon the size of the reaction vessel and its relation to the volume of the reactants, we have consistently used bomb-tubes of 20 mm. pyrex tubing with necks of 8 mm. tubing of capacity 18 cc. In all runs 5 cc. of each of the reagents were employed. The reactants were delivered into the tube while it was cooled in a CO_2 -acetone bath; the tube was then sealed off and allowed to come to room temperature. The tubes in each experiment were mounted radially on a wheel which revolved at 58 to 60 r. p. m. in a water-bath maintained at 25° (in less than 5 per cent of the reactions did the temperature vary more than 0.1°). Since the mazda light was shown to be relatively ineffective, and since the water served as a filter to the shorter wave-lengths, no special precautions were taken to shield the reaction tubes from the light of the thermostat electric bulb.

Analytical method.--After the reactions were allowed to proceed for the determined length of time (usually one hour), the bombs were removed from the water-bath, immediately frozen in CO_2 -acetone, and analyzed as follows: the contents of the tube were washed out with distilled water and twice extracted with 15 cc. portions of ether. The ether extracts were placed in a tared flask and the ether removed on a steam-bath. The water present, and any ether remaining, was taken off by placing the flask, while it was still warm, in a vacuum desiccator. The water solution still remaining, after the ether extraction, was made acid with concentrated hydrochloric acid and was again extracted with two 15 cc. portions of ether. This ether extract was treated exactly as was the first. The residue from this second ether extraction consisted of the benzoic acid formed in the reaction. From the weight of the acid it was possible to calculate the weight of benzyl alcohol formed and present in the extract of the alkaline solution, which consisted of benzyl alcohol and unchanged aldehyde. By difference the aldehyde was found and the total amount of aldehyde originally present may be calculated. From these data the extent of reaction could be determined by the following formula: $\frac{\text{m.e. acid formed}}{\text{m.e. aldehyde used}/2} \times 100 = \text{per cent reaction}$. Our analysis was further confirmed, since the weight of aldehyde delivered by the pipette was known (5.11 g., our analysis finding

this weight consistently ± 0.1 g., that is, ± 2 per cent) as well as calculated.

Irradiation.--In irradiation experiments, the source of light was usually a pyrex mercury-vapor arc. In those experiments wherein it was desired that the reaction and irradiation should proceed entirely in the absence of air, the following technique was used. Two bomb-tubes were connected by a bridge of 8 mm. tubing. In one the alkali was placed; in the other the aldehyde. The neck of one tube was sealed off, and the neck of the other was connected to the vacuum-line. While both tubes were chilled to -80° , they were evacuated to 10^{-3} mm., degassed, then re-evacuated to 10^{-5} mm. The tubes were then sealed off from the line in vacuo. The aldehyde was irradiated while the alkali was frozen. The aldehyde was either poured or distilled into the alkali, as desired; the mixture was cooled in CO_2 -acetone, and the bridge sealed off (care being exerted to avoid organic matter and consequent charring at the point of the seal). The reaction then proceeded as usual.

Duplicate experiments.--Since benzaldehyde proved to be so sensitive to various factors, blank experiments were run in every case reported.

Discussion of Results

Effect of distillation under various conditions.--Chenicek showed clearly that freshly-opened benzaldehyde reacts at a lower rate than it does after it has stood in an opened container. However, he found also that after some time the rate of reaction falls to that originally observed. Moreover, in some few cases undistilled aldehyde reacts at a higher rate in air than in vacuum. In all cases, commercial benzaldehyde reacts in an inconsistent manner: the rates for hour-long experiments vary from 15 per cent to 80 per cent. Redistilled aldehyde reacts more slowly than that not so treated, shows no air-vacuum difference in any case, and, in general, gives more consistent results. Even so, redistilled aldehyde exhibits many peculiar variations in rate if special precautions, such as those described in the experimental portion of this paper, are not taken. It seems obvious from other parts of Chenicek's work that equal emulsification must be obtained in various reactions if these various reactions are to be comparable. Since soaps are emulsifying agents, it seems plausible to us that the variations in rates

might be due to variations in the amounts of benzoic acid (and eventually potassium benzoate) present as an impurity in the different samples of benzaldehyde. We have found this to be the case.

Most methods of distillation are so rapid that the small amounts of benzoic acid present may be carried over with the aldehyde. By distilling in high-vacuum and slowly we have been able to reduce the acidity of the benzaldehyde obtained to 0.03 per cent calculated as benzoic acid. The aldehyde so obtained reacts much more slowly than other aldehydes, as well as more consistently. In the following tables it may be seen that (a) the speed and reproducibility of the reaction is dependent upon the method of distillation, (b) the aldehyde prepared in the manner described in the experimental portion of this paper is the slowest of all and reacts in the most reproducible manner, and (c) there is no air-vacuum difference (and since aldehydes form peroxides so rapidly in the air, probably no peroxide effect).

TABLE 1

RATE OF REACTION OF BENZALDEHYDE PURIFIED BY DISTILLATION^a

Method of Distillation	Usual Rate	Limits of Variation
Undistilled	30%	15-80%
Distilled at 20 mm.	25	20-40
Distilled at 10 ⁻⁵ mm., free flame	18	10-30
Distilled at 10 ⁻⁵ mm., slowly, in dark	8	4-12

^aThe results here tabulated are typical of those obtained in from 20 to 40 experiments in each set.

TABLE 2

RATE OF REACTION OF BENZALDEHYDE DISTILLED SLOWLY, IN HIGH-VACUUM IN THE DARK

Temperature of Distillation	Rate in	
	Air	Vacuum
Room temperature	9.6%	9.4%
Room temperature	7.0	4.4
70-80°	10	8
70-80°	6	8
70-80°	8,9,7,10 11,9	

A further attempt to purify the benzaldehyde by fractionation in high-vacuum proved fruitless. It was found that the acid content of each fraction, as well as its rate of reaction, was the same.

TABLE 3

RATE OF REACTION AND ACID CONTENT OF BENZALDEHYDE
FRACTIONATED IN HIGH-VACUUM

Fraction	Acid Content % Benzoic Acid by Weight ^a	Rate	
		One Hour	Three Hours
1	0.03	6	50
2	0.03	8	53
3	0.03	9	49

^aThe acid content was determined by micro-titration. The residue in the distilling vessel was so rich in benzoic acid that spontaneous crystallization took place on cooling.

It was found that concomitant with the rise in rate of reaction of the benzaldehyde which is stored in air there is a rise in acid content. As might be expected, there is no rise in rate of reaction of benzaldehyde stored in vacuum. The following table records the effect of storage in the dark. Identical results were obtained when the storage took place in diffused light.

TABLE 4

EFFECT OF STORAGE ON RATE OF REACTION

Time of Storage (Days)	Air Stored		Vacuum Stored	
	Rate	%Acid	Rate	%Acid
0	10%	0.03 ^a	10%	0.03 ^a
7	14	0.6	7	0.03 ^a
14	16	0.7	9	0.03 ^a

^aEstimated from results in Table 3. The other values are obtained by micro-titration.

Effect of benzoic acid.---Because of the above indications that benzoic acid present in benzaldehyde might act as a catalyst in the heterogeneous Cannizzaro reaction, it was decided that the effect of added benzoic acid would be studied. Using alkali salts of benzoic acid, the following results were obtained. (See Table 5, next page.)

If benzoic acid is catalytic for the heterogeneous reaction, the Cannizzaro reaction of benzaldehyde is to some extent

TABLE 5

EFFECT OF ADDED BENZOIC ACID ON THE RATE
OF REACTION OF BENZALDEHYDE

Per Cent Benzoic Acid by Weight	Rate of Reaction
0.03	8%
0.6	14
0.7	16
1.9	16
3.1	18

auto-catalytic. This is indicated by the following table, in which the reaction of pure benzaldehyde lags about one-half hour behind that of benzaldehyde containing 1 per cent added benzoic acid (in about one-half hour even the purest benzaldehyde will give rise to 1 per cent by weight of benzoic acid under the conditions used).

TABLE 6

AUTOCATALYSIS OF THE HETEROGENEOUS CANNIZZARO REACTION
OF BENZALDEHYDE

Time (Min.)	Rate of Reaction	
	Pure Aldehyde	Aldehyde with 1% Added Benzoate
20	.8%	3%
30	2.	9
60	9	17
120	21	33
180	56	78
240	79	99

In order to test our theory that the action of the benzoic acid was that of an emulsifying agent, we have tried other, more efficient, emulsifying agents in the heterogeneous reaction. In each case the action is similar to that of benzoic acid. (See Table 7, following page.)

It is possible that the results reported by Geib for the action of primary, secondary, and tertiary alcohols on the heterogeneous reaction may be due to the emulsifying action of the alcohols. cursory studies on benzyl alcohol have indicated that the effect of benzyl alcohol on the rate of reaction of benzaldehyde is somewhat less than that of benzoic acid.

TABLE 7

EFFECT OF ADDED EMULSIFYING AGENTS

Amount Material Added per 5 cc. Benzaldehyde		Rate of Reaction	
		With Addendum	Pure
0.048	g.) 1-trimethylaminostearic	25	12
0.2	) acid ^a	32	14
0.032	dimethylstearylamine oxide ...	36	16
0.152	dimethylstearylamine oxide ...	53	12
0.053	anthraquinone a-sodium sul- fonate	26	12
0.056	commercial detergent (phos- phate)	17	12
0.037	stearic acid	21	8
0.103	stearic acid	32	8
0.031	lauric acid	19	8
0.096	lauric acid	25	8

^aThe weight given is that of a 25% aqueous solution of the betaine.

The effect of irradiation on the heterogeneous Cannizzaro reaction.--When benzaldehyde is irradiated by a mercury-vapor arc, a yellow color soon appears in the liquid. This color disappears on shaking in air and there is thus some cause to believe that it may be due to the formation of free radicals. On further illumination, however, a deeper and permanent yellow color develops. Aldehyde thus treated reacts many times faster in the heterogeneous Cannizzaro reaction than that not so treated. We have found that this increase in rate is due to the formation of some new substance in the aldehyde and is not due to any reaction of the aldehyde with the air.

TABLE 8

ACCELERATION OF ALDEHYDE BY IRRADIATION

Irradiated in	Reacted in	Rate of	
		Irradiated Aldehyde	Pure
Vacuum	Vacuum	59	13
Vacuum	Vacuum	58	14
Vacuum	Vacuum	88	11
Vacuum	Air	87	9
Air	Air	100	18
Air	Air	96	10

The experiments above summarized were hour-long reactions, run as described in the experimental portion of this paper. The aldehyde was irradiated for a period of an hour at a distance of three inches from the arc.

Nature of the active agent.--We have attempted to isolate the material responsible for the acceleration. If, after irradiation (using the double-tube technique described above), the aldehyde is distilled into the alkali rather than poured over, there is no acceleration noted. However, the residue left on distillation will produce the accelerating effect. The table below, representative of some twenty experiments, summarizes this effect.

TABLE 9

EFFECT OF DISTILLATION ON IRRADIATED BENZALDEHYDE

Conditions	Rate
1. Plain reaction	11%
2. Irradiated aldehyde, poured into alkali	88
3. Irradiated aldehyde, distilled into alkali	14
4. Residue from distillation, plus pure, non-irradiated alkali and aldehyde	82

Catalytic activity of the residue.--Further experiments have shown that the residue described above contains all the catalytic activity found on irradiation. The following table, giving results of using the residue which is formed on irradiation and which is purified by removing all the benzaldehyde by distillation at 100° and 15 mm. pressure, and all the benzoic acid by washing with aqueous carbonate, emphasizes the small amounts needed to catalyze the reaction. We have also investigated the amounts of

TABLE 10

CATALYTIC EFFECT OF THE RESIDUE

Weight Residue Added to 5 cc. Aldehyde	Rate
None	11%
9.87 mg.	90
24.01 mg.	93
50.56 mg.	98

residue which are formed in aldehyde on irradiation for different periods of time. All the samples were irradiated at the same distance (three inches) from the arc, and all results indicate the weight of residue obtained, free from benzaldehyde and benzoic

acid, from 15 cc. of benzaldehyde (5 cc. were commonly used in an experiment). In this connection we have also noted that a

TABLE 11

THE RELATION OF WEIGHT OF RESIDUE TO TIME OF IRRADIATION

Time of Irradiation	Weight of Residue
15 min.	0.0234 g.
45 min.	.1215
135 min.	.3704

quartz mercury-vapor arc is about five times as effective as a pyrex arc, measured both by the amount of residue formed and the rate of reaction of the residue. On the other hand, a frosted Mazda bulb, three hundred watts, is only about one-fiftieth as effective as the pyrex arc. This is a strong indication that the effective wave-lengths are in the ultra-violet. This we have confirmed by the use of a Noviol light-yellow filter. The interposition of this filter (which absorbs all radiation shorter than $4000 \text{ \AA}^{\circ}$ and some up to $4300 \text{ \AA}^{\circ}$) effectively prevented the formation of any catalyst. Aldehyde so irradiated showed no heightened activity when compared to pure benzaldehyde.

Attempts to isolate the catalyst.--Five compounds have been found to be formed on the irradiation of benzaldehyde: benzoic acid, stilbene, benzoin, a trimer, and a tetramer. We have added all the above to pure benzaldehyde in amounts ranging from 3 to 100 mg. per 5 cc. of aldehyde and have found only benzoic acid, as described above, to have any effect whatsoever on the rate of reaction. On the other hand, the residue has been treated in such a way as to remove all the materials known to have been formed on irradiation of benzaldehyde. This residue is still so potent as to raise the rate of reaction of pure benzaldehyde 150 per cent.

In reactions involving low concentrations of alkali, we have not observed any marked catalytic effect of the residue from the distillation of irradiated benzaldehyde. In the homogeneous reaction in 70 per cent alcohol, wherein solubility considerations necessitate the use of 5 to 10 per cent alkali, there is no significant difference in the rate of reaction of pure and of irradiated benzaldehyde over a period of a week. In the heterogeneous reaction using 30 per cent alkali, pure benzaldehyde reacts to the extent of one per cent in an hour while irradiated aldehyde reacts 7 per cent. These differences lie on the outer limits of

our accuracy and we have therefore checked the results by allowing the reactions in 30 per cent alkali to run for longer periods. In a four-hour experiment, the pure benzaldehyde was found to react 6 per cent, and pure aldehyde to which residue had been added was found to react 18 per cent. This difference is significant, but is not so marked as those obtained in 50 per cent alkali.

It was found that the catalytic effect of the residue could be destroyed by heating at temperatures above 100° for hour-long periods, even in high-vacuum. This deactivation was noted during attempts to fractionate the material in a molecular still. There was little activity found in either the distillate or the residue.

An indication of the nature of the catalyst and its formation is given by the following experiments. It was found that free-radical inhibitors would also inhibit the formation of the residue. This was evinced both by the lack of residue and lack of acceleration. However, the inhibitors did not inhibit the action of the catalyst once the latter was formed, since additions of inhibitors to irradiated aldehyde did not decrease the rate of reaction.

TABLE 12

EFFECT OF ADDED INHIBITORS ON IRRADIATED BENZALDEHYDE

A. Material Added to Aldehyde before Irradiation	Rate Reaction	
	Irradiated Aldehyde plus Inhibitor	Pure Aldehyde, No Inhibitor
None	48%	12%
0.005 g. Thiophenol	10	12
0.010 g. Thiophenol	9	12
0.047 g. Thiophenol	8	14
0.067 g. Catechol	11	14
B. Material Added to Aldehyde after Irradiation	Rate Reaction of Irradiated Aldehyde	
	No Added Material	With Added Material
0.0524 g. KCN	75%	76%
0.0529 g. KNO ₃	75	74
0.0438 g. thiophenol	75	69
0.0730 g. catechol	75	73
0.0482 g. pyridine	75	73
0.01 g. beta-naphthol	72	84
0.01 g. diphenylamine	72	82

That the effect of the thiophenol during the irradiation is not that of a screen was shown by the use of a thiophenol-ligroin filter, which had no effect on the reaction whatsoever. That the reaction whereby the catalyst is not formed actually involves the thiophenol was demonstrated by the illumination of the benzaldehyde-thiophenol solution for longer periods of time. After the thiophenol was exhausted, an accelerator was finally formed.

We have established the following in the present investigation: purified aldehyde reacts at more consistent and slower rates than aldehyde ordinarily obtained; factors which have been demonstrated as raising the rate of reaction of benzaldehyde are emulsifying agents and certain unknown products of illumination with ultra-violet irradiation; the effect of ultra-violet irradiation on benzaldehyde is several times as great as that of any emulsifying agent examined and cannot be due to any of the known products of such irradiation.

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